Abstract #4000
Poster #442

Repotrectinib, a next generation TRK inhibitor, overcomes TRK resistance mutations including solvent front, gatekeeper and compound mutations

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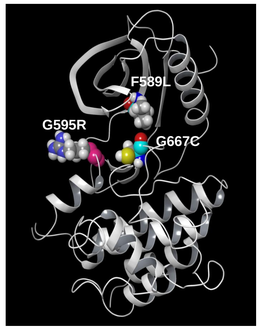
Abstract

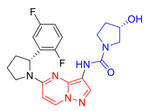
Oncogenic TRKA/B/C fusions are identified in various cancer types in adults and children. TRK inhibitors (TRKis) have demonstrated marked efficacy in patients with these cancers, however, acquired on-target resistance mediated by kinase domain mutations can occur. Next-generation TRKis targeting both wildtype and mutant TRK fusions can potentially address this unmet medical need. Repotrectinib was designed to potently inhibit wildtype (WT) TRK and overcome resistance mutations. The anti-proliferative activity of 1st generation (larotrectinib/entrectinib) and next-generation (repotrectinib/LOXO-195) TRKis were compared using engineered Ba/F3 cells expressing WT or mutated TRKs. Repotrectinib was over 10-fold more potent than LOXO-195 against WT TRK fusions and solvent front mutations (SFMs), and more than 100-fold more potent against the gatekeeper mutations TRKA F589L and TRKC F617I. Furthermore, repotrectinib was the only TRKi active against the compound mutation TRKA G595R/F589L *in cis* in preclinical Ba/F3 cells. In xenograft mouse tumor models, repotrectinib treatment led to significant tumor regression in tumors carrying WT or mutated TRK fusions. In the ongoing TRIDENT-1 phase 1 clinical trial of repotrectinib (NCT03093116), the SFMs TRKA G595R, TRKC G623R and TRKC G623E and the gatekeeper mutation TRKA F589L were detected in plasma cfDNA samples at baseline from three TRKi-resistant patients. Repotrectinib was active against ETV6-TRKC G623E in an entrectinib-resistant patient with a salivary gland tumor who achieved confirmed partial response with 9.8 months of duration of response. Tumor regression was achieved in a larotrectinib-resistant cholangiocarcinoma patient with LMNA-TRKA G595R and F589L mutations *in trans*. TRIDENT-1 is currently enrolling *NTRK* fusion-positive patients with advanced solid tumors (NCT03093116).

Introduction

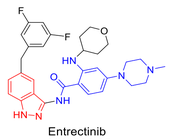


Clinical resistant mutations in TRKA

First generation TRK inhibitors

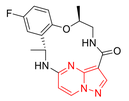


Larotrectinib
MW 428.44

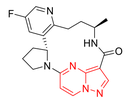


Entrectinib
MW 560.65

Next generation TRK inhibitors



Repotrectinib
MW 355.37



LOXO-195
MW 380.43

- The TRK family includes TRKA, TRKB, and TRKC proteins encoded by the genes *NTRK1*, *NTRK2*, and *NTRK3*, respectively
- Oncogenic TRK fusions that lead to constitutive activation of TRK signaling have been identified in many solid malignancies in both adults and children[1]
- 1st generation TRK inhibitors including larotrectinib and entrectinib have demonstrated clinical benefit in patients with solid malignancies harboring oncogenic *NTRK* fusions[2,3,4,5]
- Solvent front mutation, gatekeeper mutation, and glycine mutation of DFG at the beginning of the A-loop have been reported in clinical trials from larotrectinib- and entrectinib-refractory patients[2,3,4,5]
- Repotrectinib was designed to systematically overcome resistant mutations

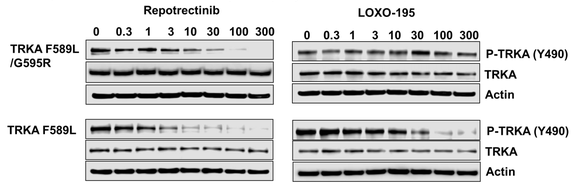
Repotrectinib potently inhibited WT and mutant TRK

Repotrectinib is the most potent TRK Inhibitor in Ba/F3 cell proliferation assays

Ba/F3 Cell Proliferation Assay IC_{50} (nM)

	LMNA-TRKA					ETV6-TRKB		ETV6-TRKC			
TRK Inhibitor[a]	WT	**G595R**	G667C	**F589L**	G595R/ F589L	WT	G639R	WT	**G623R**	**G623E**	F617I
Repotrectinib	<0.1	0.2	9.2	<0.2	13.7	<0.1	1.7	<0.2	1.0	0.6	<0.2
LOXO-195	4.6	15.1	94.9	26.5	480.8	1.4	20.8	4.0	23.9	36.1	40.9
Larotrectinib	18.9	2817	1863	597	>10000	28.2	2500	41.4	7500	1486	4000
Entrectinib	0.4	711	186.7	<0.2	1774	0.6	1577	0.8	1670	1500	54.9

[a] Other than repotrectinib, data based on evaluation of comparable proxy chemical reagents purchased from commercial sources. WT: wildtype

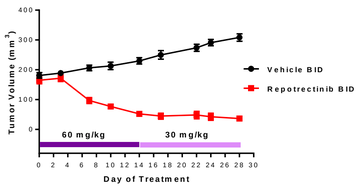


Anti-tumor effect of repotrectinib *in vivo*

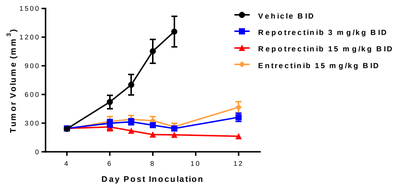
Repotrectinib demonstrated marked antitumor effects in xenograft tumor models carrying wildtype or mutated TRK fusions

- Repotrectinib was more effective than entrectinib when dosed at the same dose level of 15 mg/kg BID with statistically significant change of tumor volume (p = 0.01) in the model carrying the wildtype LMNA-TRKA fusion
- Repotrectinib was more effective than LOXO-195 when dosed at the same dose level of 30 mg/kg BID with statistically significant change of tumor volume (p = 0.03) in the model carrying the LMNA-TRKA G595R solvent front mutation
- Repotrectinib was more effective than LOXO-195 when dosed at the same dose level of 30 mg/kg BID with statistically significant change of tumor volume (p = 0.003) in the model carrying the LMNA-TRKA F589L/G595R compound mutation

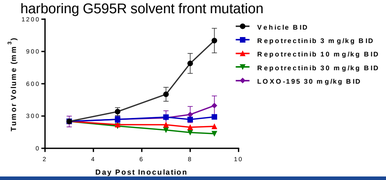
Antitumor effect of repotrectinib in patient-derived xenograft model with ETV6-TRKC fusion



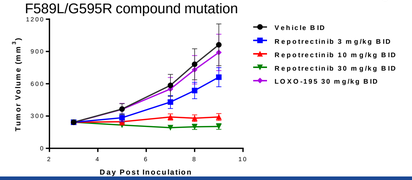
Antitumor effect of repotrectinib and entrectinib in NIH3T3 cell-derived xenograft model with LMNA-TRKA fusion



Antitumor effect of repotrectinib and LOXO-195 in NIH3T3 cell-derived xenograft model with LMNA-TRKA fusion harboring G595R solvent front mutation



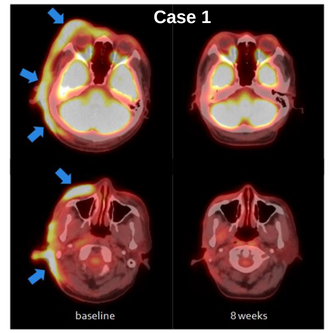
Antitumor effect of repotrectinib and LOXO-195 in NIH3T3 cell-derived xenograft model with LMNA-TRKA fusion harboring F589L/G595R compound mutation



Repotrectinib clinically inhibits resistant tumors

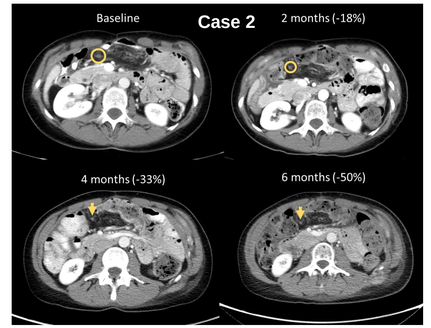
Case 1

- 51 year old Asian male
- Diagnosed with metastatic salivary gland cancer in 2013
- Treated with multiple lines of chemotherapy
- Detected ETV6-NTRK3 fusion in 2016
- Received following TKI treatments: crizotinib (duration of treatment 5.9 months, PR), entrectinib (duration of treatment 7.3 months, PR), and followed by the combination of entrectinib+MEK inhibitor with progressive disease
- Developed SFM G623E detected by tumor tissue testing while on entrectinib treatment and later also confirmed by liquid biopsy when enrolled into TRIDENT-1 trial
- Started repotrectinib at 40 mg QD (well tolerated and dose was escalated to 80 mg QD, 160 mg QD, 240 mg QD and 160 mg BID)
- Demonstrated partial response (PR) in target and cutaneous lesions after 2 months of repotrectinib treatment with 9.8 months duration of response (cPR by BICR) and 17.9 months of duration of treatment



Case 2

- 48 year old Caucasian female
- Diagnosed with metastatic cholangiocarcinoma in 2012 followed by chemotherapy
- Detected LMNA-NTRK1 fusion in 2016 and then treated with larotrectinib for 14 months with best response as PR
- Detected resistance mutations G595R and F589L (trans) by liquid biopsy when enrolled into TRIDENT-1 trial
- Started repotrectinib at 40 mg QD (well tolerated and dose was escalated to 160 mg QD at Cycle 4 per protocol)
- Achieved tumor regression of -33% after 4 months treatment with repotrectinib by Investigator assessment
- Achieved tumor regression of -50% after 6 months treatment with new lesion detected



Conclusions

- Repotrectinib was designed to bind completely inside the ATP pocket of the target kinase with greater precision and affinity and is able to target both wild type and mutant kinases
- Repotrectinib potently inhibited WT and mutant TRKs *in vitro* and *in vivo*, including the solvent front mutations which render common resistance to TRK inhibitors larotrectinib and entrectinib
- Repotrectinib is the most potent TRK inhibitor against both wildtype and mutated TRKs, especially solvent front, gatekeeper, and compound mutations in comparison with other TRK inhibitors
- Repotrectinib demonstrated antitumor effectiveness in refractory patients treated with 1st generation TRK inhibitors
- A Phase 1/2 clinical trial (TRIDENT-1) of repotrectinib is on-going for patients with advanced solid tumors harboring a *ROS1, NTRK, or ALK* fusion gene (NCT03093116)

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References

1. Vaishnavi A, et al. *Cancer Discov*. **2015**, 5(1):25-34; 2. Russo M, et al. *Cancer Discov*. **2016,** 6(1):36-44; 3. Drilon A, et al. *Ann Oncol*. **2016**, 27(5):920-6; 4. Drilon A, et al. *Cancer Discov*. **2017**, 7(9):963-972; 5.Drilon A, et al. *N. Engl. J. Med*. **2018**, 378:731-739.

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